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We're on a road to nowhere

Culture and adaptation to the environment are driving human evolution, but the destination of this journey is unpredictable

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It is tempting to believe that humans, owing to their technological prowess, have elevated themselves above the laws of biology and escaped natural selection. Indeed, some think that humans have stopped evolving at all. Another view holds that *Homo sapiens* has not isolated itself from the influences of the physical and biological world but that our species is just a special, extreme case of niche constructors.

This view is based on the so-called Niche Construction Theory, a development within evolutionary biology to describe how humans—and many other organisms—modify their environment—or niche—in a way that alters environmental pressures and therefore natural selection. Thus, rather adapting to a pre-existing environment, "organisms drive environmental change and organism-modified environments subsequently select organisms" (https://synergy.st-andrews.ac.uk/niche/niche-construction-and-evolution/) (Box 1).

Culture-driven evolution

"[All] organisms adapt to their environment, and in humans much of our environment is defined by our culture. Hence, cultural change can actually spur on adaptive evolution in humans", wrote evolutionary biologist Alan Templeton at Washington University in St. Louis, MO, USA. [1]. Following this argument, culture, social learning and technology have not replaced biological adaptation. Rather, human evolution is driven by the environmental conditions we created ourselves through culture, a process that has been accelerating since the beginning of agriculture and urban civilization. In other words, cultural niche construction is a major cause of recent human evolution.

However, there are other factors than natural selection, such as genetic drift and gene flow, that influence human evolution [1]. Nonetheless, even the effects of these random, non-adaptive forces on human genetic variation are somehow altered by cultural trends, namely increased urbanization and greater mobility. As a consequence, drift is diminishing and gene flow is increasing, a process that would eventually culminate into a single "species-wide" gene pool characterized by high levels of genetic variation.

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An alternative view of the interaction between organic and cultural evolution is considering cultural transmission as an extension of genetic inheritance [2]. "[Culture] provides a second, and extraordinarily powerful, way of evolving", wrote Richard Lenski, an expert in experimental evolution at the Michigan State University. "Genes encode information about phenotypic solutions to problems that organisms encountered in the past, and that information is transmitted only from parents to offspring. By contrast, cultural information—knowledge, technology, ideas and preferences—can be disseminated broadly, and the information can accumulate within a single generation" [http://assets.press.princeton.edu/chapters/s10711.pdf].

Yet, not everyone is convinced that humans are still evolving, at least in physical terms. In an interview with the British magazine *Radio Times*, naturalist and science broadcaster David Attenborough expressed his view that humans are the only species "to have put a halt to natural selection, of its own free will" (http://www.radiotimes.com/news/2013-09-20/david-attenborough-were-lucky-to-be-living-when-we-are-because-things-are-going-to-get-worse/). "I think", Attenborough said, "that we've stopped evolving. Because if natural selection, as proposed by Darwin, is the main mechanism of evolution—there may be other things, but it does look as though that's the case—then we've stopped natural selection. We stopped natural selection as soon as we started being able to rear 95–99% of our babies that are born".

Rather, Attenborough argued, humans would continue to evolve in a cultural sense without biological consequences. "Humans have a great cultural inheritance as well as a physical, genetic inheritance—we can inherit a knowledge of computers or television, electronics, aeroplanes and so on. Each generation has got all these books that tell them these things, so our cultural evolution is proceeding with extraordinary swiftness". His view is shared by other biologists who have expressed the idea that human evolution came to a standstill many thousands of years ago. "There's been no biological change in humans in 40,000 or 50,000 years. Every thing we call culture and civilization we've built with the same body and brain", commented Stephen Jay Gould [in 1].

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Human evolution in action

The problem is that is not easy to catch human evolution in action so as to prove either view. However, an increasing amount of evidence supports the notion that human evolution not only never stopped, but probably accelerated during the past thousands years after the emergence of *H. sapiens* as a "cultural species". A number of genes have been identified that may have indeed been shaped by cultural pressures [3], although only few well-documented examples exist. A classic one is lactose tolerance that evolved along with dairy farming. In human populations that have traditionally domesticated cattle and consumed dairy products, the ability to digest lactose persists into adulthood, while in most humans, the level of lactase declines after waning, as in other mammals. Lactase persistence would therefore result from the enrichment of alleles for lactose tolerance in pastoral communities that rely on dairy products as a staple food. Research has shown that this selection for lactase persistence began about 5,000–10,000 years ago, consistent with the onset of dairy farming [3].

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Another, more recently identified case involves human adaptation to the domestication of maize in Mesoamerica. Studies showed a strong correlation between the use of corn as the main staple food in the region and the increasing frequency of the *230Cys* allele of the ATP-binding cassette transporter A1 (*ABCA1*) in the same area [4]. The *230Cys* polymorphism is exclusively present in Native Americans and has been associated with low HDL-cholesterol levels and obesity-related comorbidities. It was suggested that the higher frequency of the *230Cys* allele might have conferred an advantage during periods of food deprivation in the past. According to the "thrifty genotype hypothesis", periods of famine during human history would generate selective pressure in favour of genetic variants that promote deposition of fat and more efficient energy use. It is thus likely that the spread of maize culture in Mesoamerica increased the frequency of gene variants such as *230Cys* in the gene pool in that region to confer an evolutionary advantage during periods of famine due to harvest loss that were frequent in ancient times [4]. The thrifty genotype hypothesis was originally developed to explain the alarming increase in type 2 diabetes and other chronic diseases in specific populations around the world as a consequence of rapid changes in lifestyle, namely shifting to high-sugar, high-calorie diet [1].

There are other findings that scientists have interpreted as proof that natural selection is still operating on present and future human populations. A team led by Philipp Mitteröcker, a theoretical biologist from the University of Vienna, Austria, caused some stirring in the field last year when they evaluated the current incidence of Caesarean sections and predicted that this surgical practice is impacting on human evolution [5].

In humans, the rate of fetopelvic disproportion—the disparity between the size of a newborn's head—which is relatively large in humans to accommodate the large brain—and the size of the maternal pelvis—is much larger compared with other primates. Biologists have long puzzled over why the female pelvis has not evolved to become wider and permit an easier birth of larger newborns, which are more healthy. The classic answer is that a wider human pelvis would be disadvantageous for bipedal locomotion, so human evolution of the female pelvis was stuck between two opposing evolutionary forces. Moreover, a wider pelvis is associated with higher risks of organ prolapse.

Mitteröcker and colleagues developed a complex evolutionary model in which only weak selection for either a narrow pelvis, a large newborn or both is sufficient to account for the high incidence of fetopelvic disproportion. In the past, women with narrow hips were more likely to die during childbirth—and thereby not passing their genes to their daughters. Thanks to Caesarean sections, slimmer women now have a much higher chance to survive childbirth; this intervention also relieves the selective force towards smaller babies. The model predicts that the advent of Caesarean sections has already led to a 10–20% increase in the rate of fetopelvic disproportion, selecting for both large neonates and women with a narrow pelvis [5]. "What does this mean for the future of humans and birth? That's not easy to foresee. Disproportion may further increase. But I don't think that one day every baby needs to be delivered by C-sections", Mitteröcker commented. "The selection towards larger babies is limited by the mother's metabolic capacity and also attenuated by modern medical treatment: also newborns with less weight or prematurely born babies have higher survival rates in industrialized countries. The same holds for wider pelvises: organ prolapse is rarely lethal nowadays. [. . .] Evolution is happening even in our modern society".

Shaped by pathogens

Infectious diseases are certainly a key evolutionary force (Fig 1). Even so, the enormous role of pathogens in human evolution cannot be fully understood without the context of anthropogenic changes to the environment. Agriculture enabled urbanization along with a drastic increase in population density and has had massive impacts on landscapes. Similarly, domestication of animals helped to increase population size and density and exposed humans to animal pathogens. "[There] is no doubt that most genetic disease in humans is due to natural selection adapting human populations to infectious agents whose selective importance was augmented, not diminished, by cultural evolution", Templeton commented [1].

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As for other hosts, our interactions with pathogens in the broader sense can be described by the so-called Red Queen hypothesis, a "winnerless" cycle of co-evolution in which both the host and the pathogens constantly evolve in response to each other. Pathogens adapt to infect the

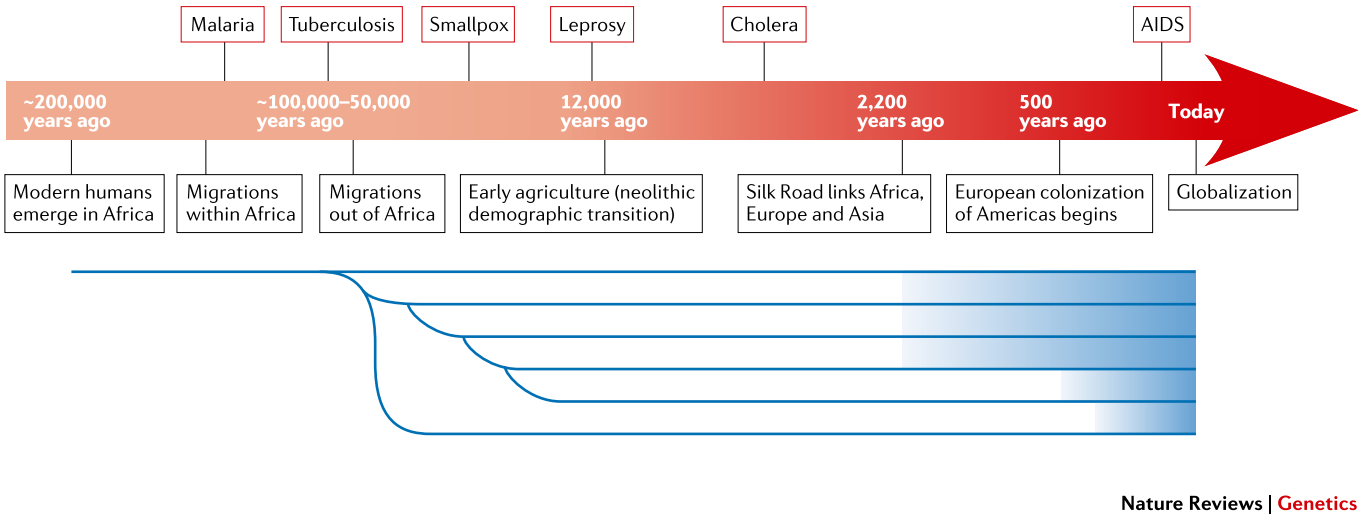


Figure 1. Infectious diseases have shaped human genome.
Pathogen emergence during human history. Reproduced from [7], with permission.

most susceptible genotypes in a host population that are therefore negatively selected against and tend to decline in frequency. Host genotypes resistant to pathogens increase in frequency, which puts pathogens under selective pressure to evolve new mechanisms that counter the increasing resistance of their host. This evolutionary process maintains genetic diversity in both host and parasite populations. In the case of humans, however, this scenario is modified by the fact that our resistance is now both encoded in the genome and cultural heritage thanks to the use of drugs and vaccines; on the other side, antibiotics and vaccines in turn alter microbial dynamics and are driving the selection of resistant strains [6].

Infectious diseases remain an important selective agent in humans even today, along with culturally induced environmental changes that create conditions for the emergence and spread of new diseases. AIDS is an example of such a recently acquired disease. It evolved from the simian immunodeficiency retroviruses (SIVs) and eventually crossed the species barrier into humans where it caused a devastating epidemic in the 1980s. Despite the relatively short time of HIV–human co-existence, there is evidence that some genetic variants that confer resistance to the virus have evolved in human populations through natural selection, the strongest signals of HIV resistance being in the MHC loci [7].

Modern population genetic studies are also providing insight into the distribution of variants that determine susceptibility to both rare and common diseases, including infectious ones, and on the evolutionary processes that shaped this part of human genetic diversity (Fig 2) [8]. "Understanding how pathogens have exerted selective pressure on human genome diversity and, more generally, on human evolution represents a highly valuable, complementary way to understand current disparities, between individuals and populations, in susceptibility to infectious diseases", said Lluis Quintana-Murci, an expert in human evolutionary genetics from the Institut Pasteur in Paris. "Understanding how natural selection, in its different forms, has impacted our genomes equals to dissecting the most natural experiment ever done, that of Nature. Evolutionary analyses will continue to bring new clues about the genetic architecture of human diseases".

However, quantifying the impact of infectious diseases on human evolution is not straightforward. "Detecting evolution in humans is trivial—our generation is obviously genetically different from our parents'—but detecting natural selection is hard", said Samuel Alizon, an expert in the evolutionary ecology of infectious disease at CNRS Institute of Ecology and the Environment in Montpellier, France. Although there are undoubtedly traces of this ancient history in our genomes, evidence of natural selection driven by infectious diseases within the past 100 years is extremely scarce, Alizon commented: "In fact, the persistence of sickle cell anaemia in regions with high malaria endemicity might be the sole solid example".

Conversely, humans also affect pathogen evolution not just by their adaption, but again by changing their environments. "Overall, a more relevant ongoing "co-evolution" is between our public health policies and the parasites we face", Alizon said. "This is where the funding should go but I agree that the research projects are more difficult to design than massive sequencing and huge genome-wide association studies". Indeed, fighting diseases has evident evolutionary implications. Medicine can be considered both a cultural achievement and a selective force that shapes the environment and thus the way we evolve. Malaria is an interesting example to illustrate this. The increase in multiple sclerosis and probably other autoimmune diseases such as type 1 diabetes in Sardinia, Italy, has been linked to the elimination of malaria from the island in the early 1950s. Centuries of exposure to *Plasmodium falciparum* would have shaped the human immune system to aggressively fight the parasite with a tendency to over-respond to triggering factors even after the disappearance of the parasites. Recent research has indeed identified a number of gene variants involved in malarial resistance and increased risk of multiple sclerosis in Sardinians (https://geneticliteracyproject.org/2017/05/01/disease-trade-off-malaria-resistance-comes-higher-risk-multiple-sclerosis-lupus/).

"Genetic adaptation to past environments with a high pathogen load is now

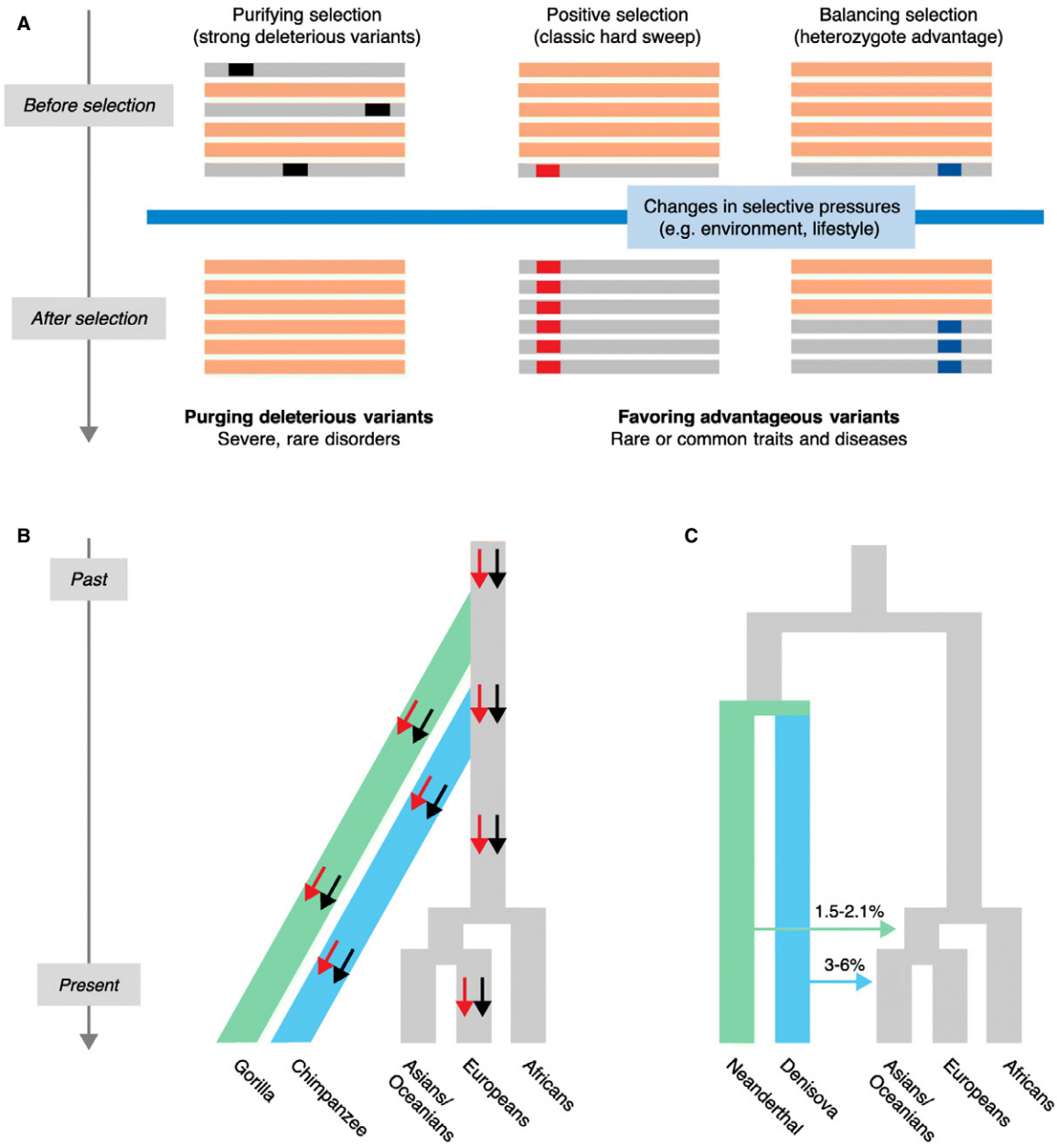


Figure 2. Selection or admixture can remove, maintain or increase genetic diversity.
(A) Schematic representation of the different types of natural selection. Purifying selection removes deleterious alleles (in black) from the population, and genes evolving under strong purifying selection are usually associated with rare, severe disorders. Conversely, mutations conferring a selective advantage (e.g. increased resistance to complex infectious disease) can increase in frequency in the population, or be maintained, through different forms of positive and balancing selection. Positive selection is represented here by the classic hard-sweep model where, following an environmental change, a newly arisen advantageous mutation or a mutation at very low frequency (in red) will be immediately targeted by positive selection and will ultimately reach fixation. Balancing selection is illustrated here by the case of heterozygote advantage (or overdominance), where the presence of heterozygotes (in blue) is favoured in the population. (B) Long-term balancing selection. Advantageous genetic diversity can be maintained over long periods of time and survive speciation, resulting in "trans-species polymorphism" (represented by black and red arrows). In this example, a trans-species polymorphism that is present in the modern European population (where it has survived the known bottleneck out of Africa) is shared with other primates, such as chimpanzees and gorillas. (C) Modern humans can also acquire genetic diversity (whether advantageous or not) through admixture with other hominins, such as Neanderthals or Denisovans. The green and blue arrows represent the direction and estimated magnitude of admixture between modern humans and Neanderthals and Denisovans, respectively. Reproduced from [8].

partly responsible for the maintenance of risk alleles for autoimmune diseases. While our ancestors were subjected to a high pressure from pathogens, these variants can cause an over-reaction of the immune system in modern sterile environments and may lead to autoimmune disorders", explained geneticist Matteo Fumagalli at the Imperial College in London, UK.

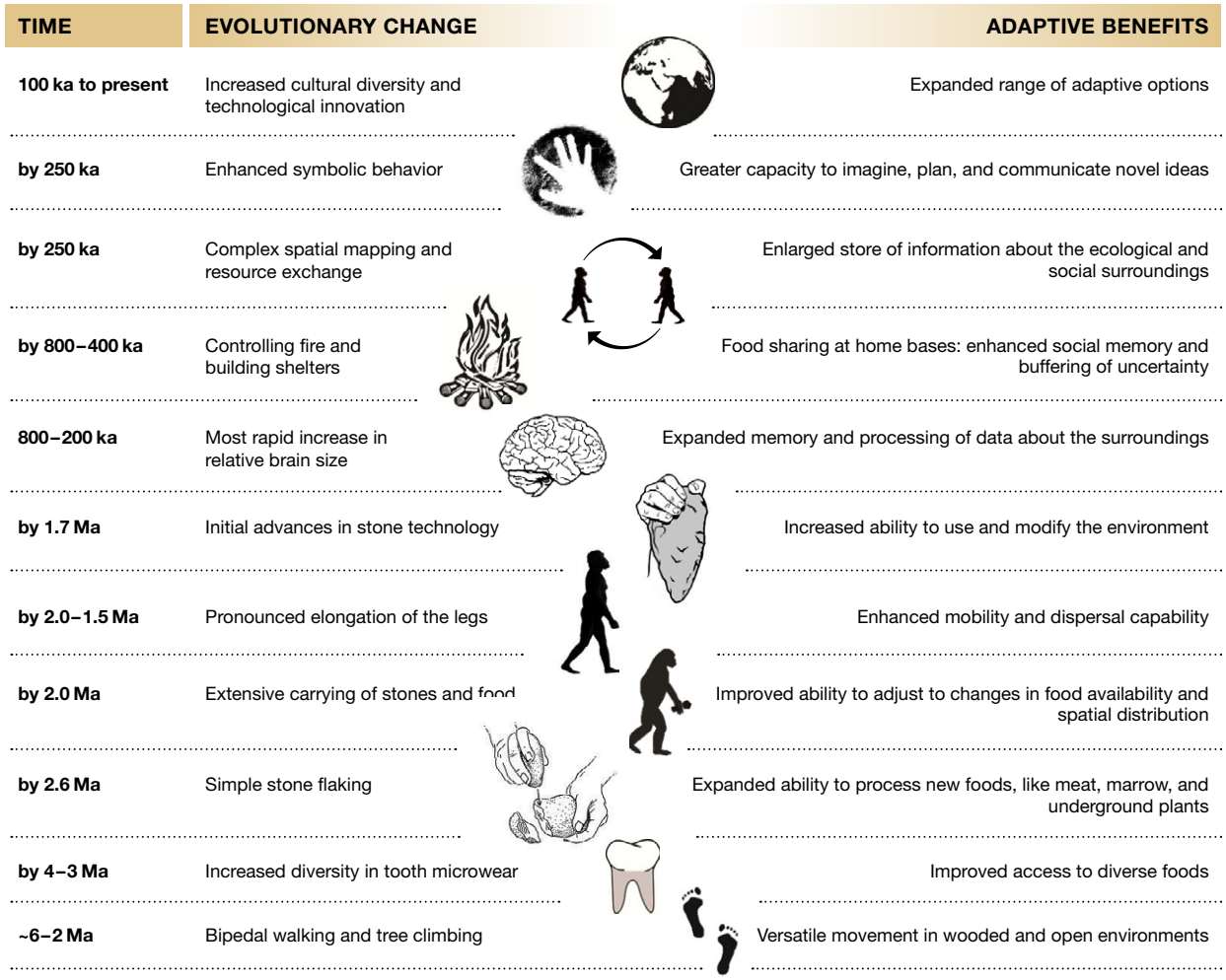


Figure 3. Important developments in human origins.
The timing of human evolutionary milestones, from 6 million years ago to present, and their adaptive benefits in terms of how they enhanced the adaptability of early human ancestors. According to the variability selection hypothesis, these major adaptations in our evolutionary history arose in response to environmental variability and shifting selection pressures (see main text for further details). Ma = million years ago; ka = thousand years ago. Source: Smithsonian Institute, *Climate effects on human evolution*, http://humanorigins.si.edu/research/climate-and-human-evolution/climate-effects-human-evolution.

"Understanding the functionality and origin of such adaptive variants has been challenging until recent years. With the advent of high-throughput sequencing machines, genomes and transcriptomes of hundreds (if not thousands) of individuals are now available to researchers. [...] By analysing the transcriptional response of monocytes in African and European individuals, recent studies showed that immune-responsive regulatory variants are preferentially targeted by natural selection".

Adapting to a changing world

While humans reshape their niche, there are other forces beyond our control that might exert a powerful and uncontrollable selective pressure, most importantly global climate change. According to Richard Potts, an anthropologist at the Smithsonian Institution in Washington, DC, USA, and Director of the Human Origins Program, climate has been a key driver of human evolution and even extinction throughout human history, and major adaptations along our evolutionary line evolved in response to environmental instability. Potts' "variability selection" hypothesis states that our *Homo* ancestors developed the ability to thrive in a wide range of habitats, rather than specializing on a particular environment (http://humanorigins.si.edu/research/climate-and-human-evolution/climate-effects-human-evolution). Comparing climate fluctuations and the timescale of key events during human evolution (Fig 3), Potts found that the latter occurred during periods of drastic environmental changes. This, over many generations, would select genes for flexibility, which allowed *Homo* to successfully adapt to changing surroundings.

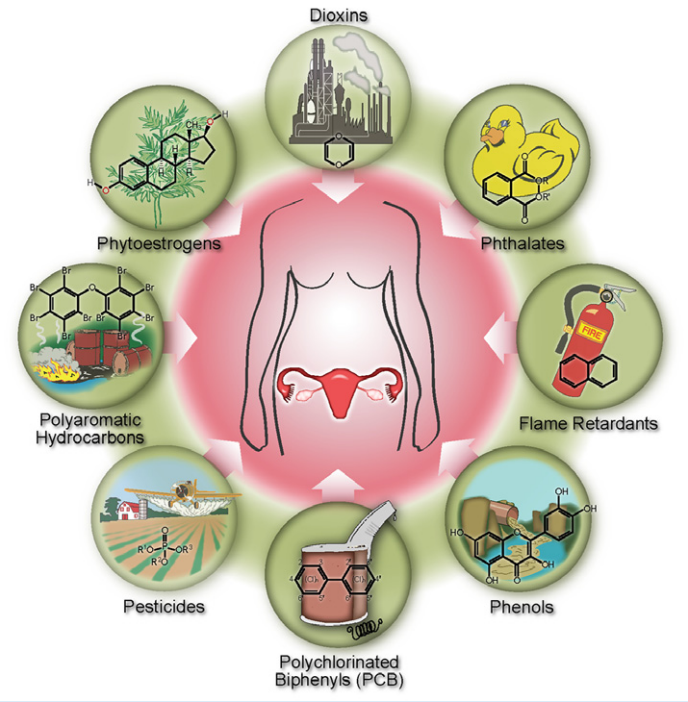
The fascinating question is therefore if and how climate change will affect human evolution in the near future as it did in the past. "When you consider the combined impact of natural climate variability and humans changing the world as part of our natural evolutionary heritage, the result is likely to affect the evolution of everything—other species certainly, and very likely a

Box 1: Endocrine disruptors and human evolution

Humans have been changing the world for millennia, and some of the man-made environmental alterations are so profound that they may leave distinctive genetic fingerprints at the population level with an evolutionary impact on our species. In particular, the ubiquitous use of endocrine disruptors—a vast array of synthetic and widely used chemicals that interfere with the endocrine system—might have some undesirable effects on human populations. These substances have been associated with perturbed reproductive function in males and females, increase in the risk of certain cancers, and severe anomalies in growth, neurodevelopment, metabolism and immunity, albeit most of these assertions are based on wildlife observations and mouse studies. Moreover, endocrine disruptors not only have lasting effects on the individual, but might also have transgenerational consequences, via epigenetic modifications.

A recent US study found a significant association between the levels of fifteen persistent endocrine disruptors and an earlier age at menopause in a large sample of women (Fig in Box 1), with menopause occurring as much as 3.8 years earlier in women with the highest levels of these chemicals in their bodies [10]. As the onset of menopause has clear implications for women's reproduction rate, endocrine disruptors might thereby influence the gene stock of future generations. Other studies have associated exposure to endocrine disruptors, possibly even in the womb, with reduced sperm quality, earlier onset of puberty, declines in fecundity and even smaller penis size.

Looking at the potential effects on human evolution, it is possible that endocrine disruptors, impacting on the reproductive success of the vulnerable ones, would, over time, select for a population more resistant to environmental chemicals. "Whereas anthropologists may have once thought that culture and technology buffered our species from evolutionary processes, repealing the laws of natural selection, we now are much more ambivalent. Rapid change in our environment, even when we ourselves are driving that change, can lead to new selective pressures, radical shifts in the forces that shape our species' survival and reproductive success", remarked Greg Downey, an anthropologist at Macquarie University in Sydney, Australia. "New elements in our constructed niches, like endocrine disrupting chemicals, can affect our evolution in quite subtle ways. Whether they will remain in our niche long enough to have substantial effect remains to be seen" (http://blogs.plos.org/neuroanthropology/2015/04/19/plastics-and-human-evolution/).



Box 1 Figure. Groups of endocrine disrupting chemicals with a potential impact on female reproduction.
Reproduced from [10].

great challenge to our own cultural adaptability", Potts commented. "It depends on whether technological progress can include the wisdom to see how mankind's activities have deep and unexpected impacts on the planet, its organisms and human cultures", he added. "If this occurs, we may be able to use our evolved capacity to alter things in ways that help the adaptability of the living systems on which human life depends".

Although it is impossible to predict the evolutionary trajectory of our species, there is room for optimism that *H. sapiens* will again adapt successfully as it has in the past. As long as human civilization does not collapse dramatically and maintains a large but sustainable global population size, our potential to evolve may remain high, given the large human gene pool. "[Because] of the large reservoir of new mutations and because culture-induced neutrality will allow greater exploration of the mutational state space, the adaptive potential of the human species as a whole will be enhanced. This may be important in adapting to global climate change", Templeton wrote [9]. Time

will tell in which direction and to which extent we will need to alter our physical and cultural environment.

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